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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,157	04/16/2004	Susan L. Lindquist	17481-003001	8571

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EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/826,157	LINDQUIST ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *23-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-22) in the reply filed on 3/6/07 is acknowledged.

Claims 23-42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/6/07.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application Nos. 60/463284 and 60/472317 filed respectively 4/16/03 and 5/20/03, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, claim 16 is drawn to a yeast cell

comprising a disruption in the PDR5 gene. However, utilization of a yeast cell comprising a disruption in PDR5 is not disclosed in the priority documents 60/463284 and 60/472317. Therefore, a priority date of 4/16/04 will be attributed to this limitation and instant claim 16.

Claim Objections

Claim 1 is objected to because of the following informalities: for accuracy, the recitation "such that induction of production of the protein is toxic to the yeast cell" should be amended to recite --wherein induction of production of the protein is toxic to the yeast cell--. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a yeast cell comprising protein or nucleic acid comprising alpha-synuclein wherein the alpha-synuclein is wild-type alpha synuclein or mutant A53T and wherein the cell comprises two integrated copies of the expression construct, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The instant claims are drawn to a yeast cells comprising nucleic acid expressing toxic levels of alpha-synuclein for purposes of establishing cells exhibiting the toxic effects of alpha-synuclein (AS). As is highly conserved among species such as mouse (see e.g. Hong et al, bridging paragraph pages 1241-1242). However, the claims are limited to use of α-synuclein peptide that is toxic to the cells. To this end the specification teaches specifically that there are only two α-synuclein peptides, wild-type (WT) and mutant A53T (see e.g. page 44, line 5-8) that are toxic to yeast cells. However, the claims are drawn broadly to any α-synuclein peptide. The state of the art of recombinant technology for the generation of fragments is highly developed. However, the ability to determine *a priori* whether a fragment or related sequence can function in the recited invention is not. As well, a review of the art demonstrates that the ability to *de novo* protein model is not routine but requires vast computation skills. As demonstrated by Smith et al, even a single mutation can greatly effect even simple structural formations of the resultant protein. This is explained in the review titled Tertiary structure that teaches mutations in genes encoding proteins can result in degradation or lack of transport or aggregation into insoluble deposits of the resulting

protein (begin page 1, last paragraph). Specifically, Tseng and Liang teach that protein surfaces in particular experience very different selective pressure than other functional domains and global protein sequence and structure similarity are often unreliable for function prediction (see Introduction). A particular protein sequence determines the protein's structural, and functional properties, and a predictability of a representative number of claimed polypeptide sequences that display noteworthy biological properties requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which a protein's structure relates to its functional usefulness (see Tertiary structure and Smith et al). Therefore, the ability to predict *a priori* which sequences that are identified following hybridization will meet a particular goal must be considered to be poorly developed.

Hence, the specification does not support the broad scope of the claims which encompass *any* yeast cell comprising protein comprising alpha synuclein that is toxic to the cells, because the specification does not establish: (A) that the genus of such proteins exist, the specification teaches in fact that there are only two such alpha-synuclein proteins that are toxic to yeast cells; (B) the specification does not provide any information on what amino acid residues are necessary and sufficient for toxic activity or to what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in a alpha-synuclein polypeptide that would preserve or improve toxicity in yeast cells. Since there are no other examples of a alpha synuclein toxic protein it is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. In Amgen Inc. v. Chugai

Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. This is the case here, where specification discloses only two peptides that meet the limitations of the claims and applicants have not provided adequate guidance as to how to identify or construct similar peptides.

Secondly, applicants have demonstrated in post-filing publications that two copies of a-synuclein are required to affect growth and cell viability (see e.g. Cooper et al, 2006, page 324, col 2 and Outeira and Lindquist, 2003, page 1773). Applicants have developed these cells to assay and analyze the toxicity of AS and absent the effect of cell growth arrest or cell viability, the ability to qualitatively determine whether a compound reverse effects depends upon the full effect of α-synuclein, which applicants own teachings indicate require two copies of α-synuclein.

Given the lack of guidance in the specification, the large and diverse group of peptides recited and the highly unpredictable nature of the art, it is concluded that a person of skill in the art would have had to conduct undue experimentation in order to practice the claimed invention.

6) Amount of Experimentation Required. The invention recites use of a broad group of alpha-synuclein peptides for screening toxic substances in a cell. Given the unpredictability of the art, the poorly developed state of the art with regard to predicting

the structural/ functional characteristics of toxic peptides encoding alpha-synuclein, the lack of adequate working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 102

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 4, 5, 6, 9, 11, 12, 17, 18, 20 and 21 are rejected under 35 U.S.C. 102(e) as being anticipated by Kim et al (US 6,858,704; see entire document) as evidenced by Lindquist et al (US 7,045,290; see entire document)

Kim et al teach yeast host cells comprising an expression construct for expression of integrated α-synuclein under control of an inducible promoter (see e.g. col 13, line 3-line 30 and col 14, line 61- col 15, line 14). As evidenced by Lindquist.et al teach that expression of WT and mutant A53T is toxic to cells (see e.g. legend to figure 3). As Kim et al teach that the peptides are comprised of full-length α-synuclein, these proteins will be inherently toxic and cause loss of cell viability and hence cell growth as recited in claims 1, 3, 4, 17 and 18. As the vector is integrated into the chromosome, the vector would inherently be required to be an integrative vector as recited in claim 9. Kim et al teach fusion proteins (see e.g. figure 1B) comprising alpha-synuclein as well as mutant (deletions) of alpha synuclein i.e. human synuclein as recited in claims 5, 6, 11, 20 and

21. Kim teaches that the fusion protein comprises a detectable protein such as an enzyme (DHFR) as recited in claim 12.

Claims 1-15 and 17-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Lindquist et al (US 7,045,290; see entire document).

The applied reference has common inventors with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Lindquist et al teach that expression of WT and mutant A53T is toxic to cells (see e.g. legend to figure 3). Lindquist teaches expression of WT and A52T in yeast cells via an integrative vector i.e. pRS304 and pRS306 for expression of alpha-synuclein (AS) as recited in claims 1, 9, 10, 17 and 18 as well as mutant and human AS as recited in claims 5, 6, 20 and 21 (see e.g. col 4, line 62- col 5, line 3). The AS may be a fusion peptide linked to a fluorescent peptide such as GFP as recited in claims 11-13. The yeast may be for example *Saccharomyces* as recited in claim 7 and 22 such as yeast cells comprising a mutation in pdr3 as recited in claims 14 and 15 (see e.g. col 10, line 28-49). As demonstrated in figure 3, the cells are non-viable (see growth characteristics in row 1 versus 2 for example. And as such, experience growth arrest as recited in claims 3 and 4. Vectors are described which allow integration of two copies or more as recited in claims

2 and 19 (see e.g. col 21) and as well comprise inducible promoters such as GPD (see e.g. col 23, line 38-60) as recited in claim 8.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lindquist et al (US 7,045,290; see entire document) as applied to claims 1-15 and 17-22 above, and further in view of Frate (US 2004/0115792; see entire document).

Applicants claim a yeast cell comprising a disrupted PDR5 gene for expression of a toxic amount of a-synuclein.

The teachings of Lindquist et al are described above and are applied as before except; Lindquist et al do not teach use of a cell comprising a disruption in PDR5.

Frate teaches use of a yeast cell line comprising a disruption of PDR5 for testing genotoxicity and cytotoxicty of environmental contaminants. Frate chose use of this cell line as genes are responsible for export of toxic substances from the cell and their deletion means that toxic compounds can be analyzed in the context of the cell (see e.g. ¶ 0066-0067).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cells comprising a deletion in pdr3 as taught by Lindquist et al with the cells comprising a pdr5 deletion as taught by Frate because

Lindquist et al teach that it is within the skill of the art to assess toxicity of substances in a yeast cell expressing alpha-synuclein and because Frate teaches that it is within the ordinary skill of the art to use a pdr5 deficient cell as a host cell for analysis of toxic compounds. One would have been motivated to do so in order to receive the expected benefit of unhampered comparison of cell line as genes are responsible for export of toxic substances from the cell and their deletion means that toxic compounds can be analyzed in the context of the cell. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Examiner
Art Unit 1633